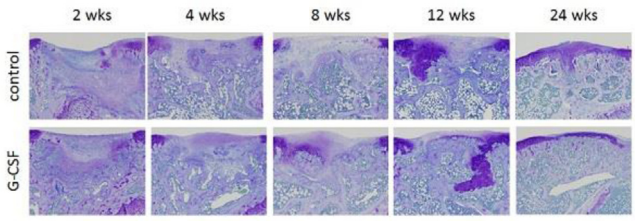

Figure: toluidine blue staining

test. Statistical tests were considered significant at the level of $P < 0.05$. All P-values were 2-sided.

Results: The number of peripheral blood leukocytes started to increase at day 3 and returned to normal levels at day 7 after the first injection. Moreover, histology showed the G-CSF group had more fibrous and/or bony tissue at earlier time point (Figure). The tissue repair rate was significantly higher in the G-CSF group 4 weeks after surgery. However, the cartilage repair rate and modified Wakitani score were not significantly different between the two groups at each time point.

Conclusions: The defect filling was significantly better in the G-CSF group in the early phase. G-CSF could act as a promoting agent in the repair of osteochondral defects by increasing the number of peripheral blood nucleated cells. Better cartilage repair might be expected if the higher number of peripheral blood nucleated cells could be maintained for a longer time than that in our experiment.

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INTRA-ARTICULAR TREATMENT WITH RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN 7 (BMP-7) ATTENUATES THE DEVELOPMENT OF OSTEOARTHRITIS IN A SURGICALLY INDUCED RAT MODEL

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Purpose: Several experimental animal models have been developed for human osteoarthritis (OA) and used to study the preclinical efficacy of disease and symptom modifying OA drug candidates. One of these candidates is recombinant human bone morphogenetic protein 7 (rhBMP-7). It is a bone-inducing agent used currently in clinical practice to enhance bone formation in spinal fusions and during fracture repair. In preclinical studies, rhBMP-7 has been shown to attenuate the development of degenerative changes induced by anterior cruciate ligament transection in rabbits and by excessive running in rats and to repair cartilage damage in rabbits, goats, sheeps and dogs. In this study, we characterized the effects of rhBMP-7 treatment on the development of OA induced by medial meniscal tear (MMT) and medial collateral ligament transection (MCLT) in rats.

Methods: The study was conducted using male Lewis rats (body weight range 360-425 g). Unilateral OA was induced in their knee joints by surgical MMT and MCLT operation. Treatment of animals was started one week after the operation and continued once a week for 5 weeks. Animals were treated intra-articularly with rhBMP-7 at the dose of 0.25 μg/wk and with vehicle at the dose of 0.05 ml/wk. Treatment effects on body weight and OA symptoms were followed during the study. Joint discomfort and pain were used as OA symptoms. They were determined as static weight bearing and static mechanical allodynia and analyzed as hind paw weight distribution using Incapacitance Tester and paw withdrawal threshold using von Frey filaments, respectively. After 6 post-surgery weeks, animals were terminated and treatment effects on knee joints were determined histologically following the recommendations of the Osteoarthritis Research Society International (OARSI) histopathology initiative. This experimental protocol was approved by the national Animal Experiment Board, Regional State Administrative Agency for Southern Finland, Hämeenlinna, Finland.

Results: Body weight was decreased in operated animals and paw weight bearing and paw withdrawal threshold were decreased in operated hind limbs after the first post-surgery week when compared with non-operated control animals. This demonstrated the presence of joint discomfort and pain in operated animals at the beginning of treatment. Body weight, paw weight bearing and paw withdrawal threshold were decreased in operated animals treated with vehicle also after 3 post-surgery weeks. Intra-articular treatment with rhBMP-7 at the dose of 0.25 μg/wk improved paw weight bearing and increased paw withdrawal threshold when compared with vehicle. Microscopic assessment of OA demonstrated from mild to marked degenerative changes in the medial compartment of operated knee joints in animals treated with vehicle. These degenerative changes included the loss of chondrocytes, proteoglycans and collagen matrix from superficial layer down to tidemark in medial tibial plateau and the presence of large osteophytes and moderate synovial inflammation. The loss of chondrocytes and collagen matrix was pronounced on the outer 1/3 of the medial tibial plateau. Almost similar lesions were observed in the middle 1/3 and less severe lesions in the inner 1/3 of the plateau. The microscopic assessment of OA demonstrated from non-generation to marked generative changes in operated animals treated with the intra-articular rhBMP-7 dose of 0.25 μg/wk. Treatment with rhBMP-7 decreased the width of significant cartilage degeneration in the medial tibial plateau and reduced the severity of chondrocyte and collagen matrix lesions in the middle and inner 1/3 of the plateau when compared with vehicle.

Conclusions: This study characterized the effects of rhBMP-7 treatment on the development of OA in the rat MMT+MCLT model used frequently in the preclinical efficacy studies of disease and symptom modifying OA drug candidates. Intra-articular treatment with rhBMP-7 at the dose of 0.25 μg/wk decreased the width of significant cartilage degeneration and reduced the severity of chondrocyte and collagen matrix lesions focally. These results indicated a chondroprotective activity for intra-articular rhBMP-7 in the rat MMT+MCLT model and support the development of rhBMP-7 as a potential drug candidate for human OA in clinical trials.

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A REVIEW ON CURRENT ANIMAL MODELS OF OSTEOARTHRITIS RESEARCH; PAVING THE WAY FOR THE DEVELOPMENT OF NOVEL DISEASE-MODIFYING ANTI-OSTEOARTHRITIC AGENTS

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Purpose: Osteoarthritis (OA) is one of the most prevalent chronic conditions worldwide. Pathogenesis of idiopathic OA has not yet been fully understood. The time course of disease onset is slow and disease progression is extremely variable. Therefore, the development of OA is difficult to study in humans, and animal models seem to be invaluable research tools that enable the researchers not only to further their understanding of disease pathogenesis but also to pave the way for the development of novel therapeutic agents. The present study aims to review available OA animal models and induction mechanisms. Advantages and disadvantages of the species commonly used and OA induction methods will also be discussed in detail.

Methods: The researchers reviewed available OA animal models and induction mechanisms including intra-articular injections of enzymes, and chemicals as well as surgical inductions of OA. Literature searches were conducted on electronic databases, and the following MeSH terms were used: Osteoarthritis animal models, Osteoarthritis Induction Mechanisms, Papain, Collagenase, Hyaluronidase, Monosodium Iodoacetate, Anterior Cruciate Ligament Transection (ACLT), and Meniscectomy.

Results: Enzymatically/ chemically induced OA models have found to exhibit various effects on joint physiology. Papain and Monosodium Iodoacetate have found to specifically alter chondrocyte metabolism and induce significant chondrocyte apoptosis and joint inflammation; whereas, collagenase-induced models showed histological damages to ligaments and tendons. However, some studies were skeptical regarding the use of Monosodium Iodoacetate induction method for pathophysiological studies of human OA. Cartilage degeneration in collagenase-induced models is thought to be associated with the direct ingestion of collagen in cartilage and the inflammatory reaction in the joint tissue. However, studies suggested that genetic differences in the composition of proteoglycans and arrangement of collagen fibers may influence the sensitivity of the cartilage. Surgically-induced animal models (ACLT, and Meniscectomy) were found to be one of the most widely used OA induction methods. In comparison with other OA induction methods, surgically-induced OA showed a higher disease onset and disease severity. Most studies reported sequential events of